DETAILED ACTION

Status of the Claims

Claims 38-39, 44, and 47 were canceled in the amendment to the claims received on February 15, 2006.

Claims 22-23, 28-37, 40-43, 45-46, and 48-49 were canceled and claims 1-2, 7, 9, 10, 14, 21, and 24-27 were amended in the amendment to the claims received on August 25, 2006.

The amendment to the claims received on November 19, 2007 amended claim 1.

The amendment to the claims received on August 20, 2008 amended claims 1-6, 8, 14, and 26-27 and canceled claim 25.

The amendment to the claims received on February 19, 2009 changed the status identifiers only.

The amendment to the claims received on June 10, 2009 amended claim 1.

The amendment to the claims received on January 10, 2011 amended claim 1.

The amendment to the claims received on August 9, 2011 amended claims 1, 13, 14, and 17 and canceled claim 18.

The amendment received on December 23, 2011 amended claims 1, 3-6, 13, 14, 17, 21, 26, and 27 and added new claim 50.

Claims 1-17, 19-21, 24, 26-27, and 50 are currently pending.

Claims 1-11, 13-14, 17, 21, 24, 26-27, and 50 are currently under consideration.

Election/Restrictions

Applicant elected, with traverse, antibody as the species of binding molecule, C-terminal motif as the species of motif, and at least 10% as the species of capture in the reply filed on

February 15, 2006. Claims 12, 15-16, and 19-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected species, there being no allowable generic or linking claim.

Priority

The present application claims priority to U.S. provisional application 60/454,229 filed March 12, 2003.

Withdrawn Objections

The objections to claims 1-11, 13, 14, 17, 21, 24, 26, and 27 are withdrawn in view of the amendment received on December 23, 2011.

Withdrawn Rejections

The rejection to claims 1-11, 13, 14, 17, 21, 24, 26, and 27 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the support provided by applicants in the response received on December 23, 2011.

The rejection to claims 1-11, 13, 14, 17, 21, 24, 26, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the claim amendments received on December 23, 2011.

Maintained Rejections

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11, 13-14, 21, 24, and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Minden et al. WO 02/086081 A2 (filing date April 22, 2002), Nelson et al. U.S. Patent 6,887,713 (effective filing date of March 11, 2000), and Kumar U.S. Patent Application Publication 2002/0110835 published August 15, 2002.

For present claim 1, Minden et al. teach methods of identifying a protein via assigning (i.e. separating) binding reagents to designated locations on an array, detecting the binding patterns, and comparing the binding pattern to a reference set (i.e. characterizing; please refer to the abstract, paragraphs [0005-0012], [0028-0032], [0035-0044], [0072-0074], [0077], [00117], Figures 1-11, and Table 1). In addition, Minden et al. teach that the molecular weight or mass of the binding reagents can be determined and that spectrometry can be utilized (please refer to paragraphs [0003-0004], [0030], [0036], [0048]; Figures 7-9). Furthermore, Minden et al. teach that more than one protein can have the same epitope thus the common epitopes (i.e. more than one) would bind to the same defined location (please refer to Figures 4A-4C and 5 and paragraphs 89-96). In addition, Minden et al. teach that the binding reagents can be antibodies (please refer to paragraphs [0029], [0056-0061], [0072]). Minden et al. discuss utilizing mass spectrometry in methods of identifying proteins (i.e. utilizing mass spectrometry in both homogenous and heterogeneous methods; paragraphs 3-4 and 136). Furthermore, Minden et al. teach heterogeneous protein mixtures including proteolytic cleavage of proteins (please refer to paragraphs 29-35). Moreover, Minden et al. teach that the protein mixture can be all of the proteins in a given organism, proteome, organ, tissue, cell, organelle, or sub-cellular localization

(see paragraph 35) and thus all of the proteins are not necessarily known. Minden et al. teach that the array can have 2-100 different proteins (please refer to paragraphs [0047], [0073-0074]).

For present claim 2, Minden et al. teach that the total protein content of a cell or tissue can be utilized as the protein mixture (please refer to paragraphs [0035], [0066]).

For present claims 3-6, Minden et al. teach that the protein mixture can be fragmented with various chemical or enzymatic methods including trypsin (please refer to paragraph [0037-0039], [0066], [00105], [00107], and Table 1).

For present claims 7-8 and 11, Minden et al. teach that trypsin cleavage forms a peptide or epitope (i.e. motif) with C-terminal lysine or arginine residues (please refer to Table 1 and paragraphs [0041-0045], [0049], [0054], [0063]).

For present claims 9-10, Minden et al. teach that the peptides or epitopes (i.e. motifs) can be at least three amino acids in length and can have at least two variable amino acids (please refer to paragraphs [0029], [0032], [0040-0046], [0054], [00113-00116]).

For present claim 13, Minden et al. teach that arrays can have different binding molecules at spatially addressable locations which bind to different binding reagents (please refer to paragraphs [0005], [0008], [0012], [0028], [0040]).

For present claim 14, Minden et al. teach that the protein mixture may comprise all (i.e. at least 10% of the peptides) of the proteins and that the epitopes cover the binding mixture (please refer to paragraph [0035], [0040]).

For present claim 21, Minden et al. teach that the proteins are compared to a reference set (i.e. characterizing; please refer to paragraphs [0005], [0028-0031], [0040]).

For present claim 27, Minden et al. teach that various binding reagents can be compared to a reference set or to other binding reagents (please refer to paragraphs [0005], [0030-0031, [0040], [0053]).

However, Minden et al. does not specifically teach determining the abundance of the proteins by the use of desorption mass spectrometry or collision induced dissociation mass spectrometry.

For present claims 1, 24, and 26, Nelson et al. teach analyzing complex biological mixtures utilizing "lab-on-a-chip" (i.e. chip-based microarrays) and MALDI-TOF (i.e. combination of both desorption mass spectrometry and collision induced dissociation mass spectrometry) wherein the proteins are quantified (i.e. abundance), internal reference standards are utilized, and determining the amount (i.e. abundance) of the proteins (please refer to the entire specification particularly the abstract; Figures 1, 4, 7, 8a-c, and 10a-c; column 1, lines 54-67; columns 2-3; column 4, lines 1-30; column 6, lines 52-67; column 8, lines 19-64; column 9, lines 13-35; columns 10-11 and 14-15; column 16, lines 1-10; column 17, lines 30-45). Nelson et al. discuss utilizing mass spectrometry in methods of identifying proteins (i.e. utilizing mass spectrometry in both homogenous and heterogeneous methods; columns 9-10). Nelson et al. teach utilizing MALDI-TOF for quantitative analysis including analysis of proteins from biofluids, heterogeneous analyte systems, sample comprising point mutations, etc. (i.e. heterogeneous sample; see column 2, lines 42-46; paragraph spanning columns 3-4; columns 5, 8-11, 15-16; Examples 3 and 6).

While Minden et al. discusses utilizing antibodies as binding reagents and immobilization of binding reagents onto arrays or substrates (see paragraphs 28 and 29), the specific examples provided by Minden et al. have the proteins, peptides, etc. immobilized on the array.

For present claims 1, 24, 26, and 27, Kumar teaches proteomic analysis comprising providing a substrate comprising distinct spots or deposits including an array of antibodies, exposing the antibody array to a sample containing proteins to allow capture of specific proteins, and subsequently interfacing the substrate (i.e. antibody array with bound proteins) with a MALDI-TOF instrument for identification of the proteins captured on the substrate/antibody array (please refer to the entire specification particularly abstract; paragraphs 27, 33, 37; Example 1).

The claims would have been obvious because the substitution of one known element (i.e. mass spectrometry providing mass information only as taught by Minden et al.) for another (i.e. mass spectrometry providing both mass and abundance information; MALDI-TOF as taught by Nelson et al. and Kumar) would have yielded predictable results (i.e. analysis of both mass and abundance at the same time) to one of ordinary skill in the art at the time of the invention and/or (b) the claim would have been obvious because a particular known technique (i.e. MALDI-TOF utilized to determine mass and abundance of proteins bound to antibody arrays) was recognized as part of the ordinary capabilities of one skilled in the art. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

Therefore, the teaching of Minden et al., Nelson et al., and Kumar render the presently claimed invention *prima facie* obvious.

Arguments and Response

Applicants' arguments directed to the rejection under 35 USC 103 (a) as being unpatentable over Minden et al., Nelson et al., and Kumar for claims 1-11, 13-14, 21, 24, and 26-27 were considered but are not persuasive for the following reasons.

Applicants contend that the array disclosed by Minden et al. is an antigen array format not an antibody array format (applicants provide both prior and post filing art to show that both antigen arrays and antibody arrays were well known in the prior art, but considered different in both the prior and post filing art). In addition, applicants contend that Minden et al. only discuss hypothetical proteins with epitopes in common (i.e. not "specifically binding to a single motif that is present in greater than 2 different types of proteins, peptides, protein fragment or peptide fragment"). Applicants contend that there is "no substantiation of whether these hypothetical proteins are different proteins or whether they are merely variants of the same protein". In addition, applicants suggest that the only disclosure in Minden et al. to mass spectrometry is to caution regarding the expense and specialized skills required.

Applicants' arguments are not convincing since the teachings of Minden et al., Nelson et al., and Kumar render the method of the instant claims *prima facie* obvious.

It is respectfully noted that the presently claimed invention requires "antibodies or fragments thereof fixed to spaced apart defined locations on an array" and "proteins, peptides, protein fragments or peptide fragments". Thus, one of skill in the art when applying the broadest reasonable interpretation would read "antibodies or fragments thereof" to encompass full antibodies (i.e. VH, VL, constant region), Fab, scFv, VH, VL, Fc, CDR1, CDR2, CDR3, FR1, FR2, FR3, FR4, etc. (i.e. wherein antibody fragment could be an antigen itself, e.g. antibodies

which bind Fc, anti-idiotypic antibodies, etc.) and "proteins, peptides, protein fragments or peptide fragments" to encompass antibodies (e.g. antibodies are proteins, CDR3 is a peptide, etc.). During patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See *In re Morris*, 127 F.3d 1048, 44 USPQ2d 1023 (Fed. Cir. 1997).

Regarding applicant's assertion that "antibodies are understood to bind a specific target and one skilled in the art would not expect one antibody to bind multiple proteins", it is respectfully noted that the same motif found in different proteins is what is being bound in the present invention. In addition, a monoclonal antibody (i.e. binds a single specific epitope/motif/antigen) may bind a single motif present in different proteins, polyclonal antibodies bind more than one motif/epitope/antigen, etc. In addition, it is respectfully noted that the presently claimed invention requires binding (i.e. encompassing nonspecific binding) and not specific binding, a specific Kd, etc.

Regarding applicants statement that there is "no substantiation of whether these hypothetical proteins are different proteins or whether they are merely variants of the same protein" (in Minden et al.), it is respectfully noted that present specification defines "different type" as including proteins and peptides differing in amino acid sequence, mass, posttranslation modifications and the like (i.e. encompassing variants, see page 5 lines 3-6 of the present specification).

"The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." See *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ

1038, 1039 (Fed. Cir. 1983) and *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. See *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989), *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005), and *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir.1998). Minden et al. teach methods comprising cleaving the protein with a proteolytic agent to produce peptide fragments, providing an array comprising a solution set of binding reagents, contacting the peptide fragments with the array to promote specific interactions, detecting the binding pattern, and comparison to a reference set wherein the "binding reagents" can be antibodies, Fv, scFv, Fab (i.e. array of antibodies; please refer to the entire specification particularly paragraphs 5, 29, 72). Minden et al. teach "a solution set of binding reagents may be designed to recognize a set of epitopes that are shared by many proteins in such a way that the set of epitopes covers and is capable of distinguishing proteins in the protein mixture" (see paragraph 40).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Kumar teaches antibody microarrays and interfacing the microarrays with MALDI-ToF (see paragraphs 27, 33, etc.). Nelson et al. teach bioactive chip mass spectrometry utilizing antibody chips, capturing

proteolytic analyte fragments, and mass spectrometry analysis including MALDI-ToF (see abstract, Figure 1, column 1, etc.).

Claims 1-11, 13-14, 21, 24, and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Minden et al. WO 02/086081 A2 (filing date April 22, 2002), Barry et al. WO 0225287 (filed September 19, 2001), and Kumar U.S. Patent Application Publication 2002/0110835 published August 15, 2002.

For present claim 1, Minden et al. teach methods of identifying a protein via assigning (i.e. separating) binding reagents to designated locations on an array, detecting the binding patterns, and comparing the binding pattern to a reference set (i.e. characterizing; please refer to the abstract, paragraphs [0005-0012], [0028-0032], [0035-0044], [0072-0074], [0077], [00117], Figures 1-11, and Table 1). In addition, Minden et al. teach that the molecular weight or mass of the binding reagents can be determined and that spectrometry can be utilized (please refer to paragraphs [0003-0004], [0030], [0036], [0048]; Figures 7-9). Furthermore, Minden et al. teach that more than one protein can have the same epitope thus the common epitopes (i.e. more than one) would bind to the same defined location (please refer to Figures 4A-4C and 5 and paragraphs 89-96). In addition, Minden et al. teach that the binding reagents can be antibodies (please refer to paragraphs [0029], [0056-0061], [0072]). Minden et al. discuss utilizing mass spectrometry in methods of identifying proteins (i.e. utilizing mass spectrometry in both homogenous and heterogeneous methods; paragraphs 3-4 and 136). Furthermore, Minden et al. teach heterogeneous protein mixtures including proteolytic cleavage of proteins (please refer to paragraphs 29-35). Moreover, Minden et al. teach that the protein mixture can be all of the

proteins in a given organism, proteome, organ, tissue, cell, organelle, or sub-cellular localization (see paragraph 35) and thus all of the proteins are not necessarily known. Minden et al. teach that the array can have 2-100 different proteins (please refer to paragraphs [0047], [0073-0074]).

For present claim 2, Minden et al. teach that the total protein content of a cell or tissue can be utilized as the protein mixture (please refer to paragraphs [0035], [0066]).

For present claims 3-6, Minden et al. teach that the protein mixture can be fragmented with various chemical or enzymatic methods including trypsin (please refer to paragraph [0037-0039], [0066], [00105], [00107], and Table 1).

For present claims 7-8 and 11, Minden et al. teach that trypsin cleavage forms a peptide or epitope (i.e. motif) with C-terminal lysine or arginine residues (please refer to Table 1 and paragraphs [0041-0045], [0049], [0054], [0063]).

For present claims 9-10, Minden et al. teach that the peptides or epitopes (i.e. motifs) can be at least three amino acids in length and can have at least two variable amino acids (please refer to paragraphs [0029], [0032], [0040-0046], [0054], [00113-00116]).

For present claim 13, Minden et al. teach that arrays can have different binding molecules at spatially addressable locations which bind to different binding reagents (please refer to paragraphs [0005], [0008], [0012], [0028], [0040]).

For present claim 14, Minden et al. teach that the protein mixture may comprise all (i.e. at least 10% of the peptides) of the proteins and that the epitopes cover the binding mixture (please refer to paragraph [0035], [0040]).

For present claim 21, Minden et al. teach that the proteins are compared to a reference set (i.e. characterizing; please refer to paragraphs [0005], [0028-0031], [0040]).

For present claim 27, Minden et al. teach that various binding reagents can be compared to a reference set or to other binding reagents (please refer to paragraphs [0005], [0030-0031, [0040], [0053]).

However, Minden et al. does not specifically teach determining the abundance of the proteins by the use of desorption mass spectrometry or collision induced dissociation mass spectrometry.

Barry et al. teach methods of determining the binding and mass of trypsin digested proteins including antibodies from a cell including phage or tissue sample immobilized on an array (please refer to the abstract, pages 2-6, 21-30, Figures 3-6 and 8-10, Examples 2-3).

For present claim 1, Barry et al. teach determining the abundance of proteins via MALDI-TOF (i.e. mass; please refer to pages 5-6, page 32, lines 25-33, page 33, lines 21-37, pages 34-35, Figures 3-6 and 8-10, Examples 2-3). Barry et al. discuss utilizing mass spectrometry in methods of identifying proteins (i.e. utilizing mass spectrometry in both homogenous and heterogeneous methods; pages 33-35). Barry et al. teach quantitative or semi-quantitative analysis via MALDI-TOF wherein the sample can include body fluid, tissue, or cell (i.e. heterogeneous; please refer to pages 3, 9, 21, 28, 32-34, 45-46).

For present claim 24, Barry et al. teach MALDI-TOF (i.e. matrix assisted laser desorption ionization-time of flight) mass spectrometry (i.e. combination of both desorption mass spectrometry and collision induced dissociation mass spectrometry or CID; page 35, line 7; please refer to pages 5-6, page 32, lines 25-33, page 33, lines 21-37, pages 34-35, Figures 3-6 and 8-10, Examples 2-3).

For present claim 26, Barry et al. teach determining the abundance of the protein via MALDI-TOF including proteins from any given starting material (i.e. unfragmented parent protein; please refer to page 3, lines 28-30; pages 5-6; page 32, lines 25-33; page 33, lines 21-37; pages 34-35; Figures 3-6 and 8-10, Examples 2-3).

While Minden et al. discusses utilizing antibodies as binding reagents and immobilization of binding reagents onto arrays or substrates (see paragraphs 28 and 29), the specific examples provided by Minden et al. have the proteins, peptides, etc. immobilized on the array.

For present claims 1, 24, 26, and 27, Kumar teaches proteomic analysis comprising providing a substrate comprising distinct spots or deposits including an array of antibodies, exposing the antibody array to a sample containing proteins to allow capture of specific proteins, and subsequently interfacing the substrate (i.e. antibody array with bound proteins) with a MALDI-TOF instrument for identification of the proteins captured on the substrate/antibody array (please refer to the entire specification particularly abstract; paragraphs 27, 33, 37; Example 1).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of identifying proteins taught by Minden et al. with the MALDI-TOF analysis taught by Barry et al.

One having ordinary skill in the art would have been motivated to do this because Barry et al. teach that the use of mass spectrometry and MALDI-TOF provide semi-quantitative and quantitative results for protein microarrays (please refer to page 1, lines 20-26 and 34-37; page 2, lines 1-24; page 3, lines 5-30; Examples 2-3).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the method of identifying proteins taught by Minden et al. with the MALDI-TOF analysis taught by Barry et al. because of the examples provided by Barry et al. show that trypsin digested antibody arrays can be quantitated via MALDI-TOF (please refer to Examples 2-3).

The claims would have been obvious because the substitution of one known element (i.e. mass spectrometry providing mass information only as taught by Minden et al.) for another (i.e. mass spectrometry providing both mass and abundance information; MALDI-TOF as taught by Barry et al. and Kumar) would have yielded predictable results (i.e. analysis of both mass and abundance at the same time) to one of ordinary skill in the art at the time of the invention and/or (b) the claim would have been obvious because a particular known technique (i.e. MALDI-TOF utilized to determine mass and abundance of proteins bound to antibody arrays) was recognized as part of the ordinary capabilities of one skilled in the art. See KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007).

Therefore, the modification of the method of identifying proteins taught by Minden et al. with the MALDI-TOF analysis taught by Barry et al. and Kumar render the instant claims *prima facie* obvious.

Arguments and Response

Applicants' arguments directed to the rejection under 35 USC 103 (a) as being unpatentable over Minden et al., Barry et al., and Kumar for claims 1-11, 13-14, 21, 24, and 26-27 were considered but are not persuasive for the following reasons.

Applicants contend that the array disclosed by Minden et al. is an antigen array format not an antibody array format (applicants provide both prior and post filing art to show that both

antigen arrays and antibody arrays were well known in the prior art, but considered different in both the prior and post filing art). In addition, applicants contend that Minden et al. only discuss hypothetical proteins with epitopes in common (i.e. not "specifically binding to a single motif that is present in greater than 2 different types of proteins, peptides, protein fragment or peptide fragment"). Applicants contend that there is "no substantiation of whether these hypothetical proteins are different proteins or whether they are merely variants of the same protein". In addition, applicants suggest that the only disclosure in Minden et al. to mass spectrometry is to caution regarding the expense and specialized skills required.

Applicants' arguments are not convincing since the teachings of Minden et al., Barry et al., and Kumar render the method of the instant claims *prima facie* obvious.

It is respectfully noted that the presently claimed invention requires "antibodies or fragments thereof fixed to spaced apart defined locations on an array" and "proteins, peptides, protein fragments or peptide fragments". Thus, one of skill in the art when applying the broadest reasonable interpretation would read "antibodies or fragments thereof" to encompass full antibodies (i.e. VH, VL, constant region), Fab, scFv, VH, VL, Fc, CDR1, CDR2, CDR3, FR1, FR2, FR3, FR4, etc. (i.e. wherein antibody fragment could be an antigen itself, e.g. antibodies which bind Fc, anti-idiotypic antibodies, etc.) and "proteins, peptides, protein fragments or peptide fragments" to encompass antibodies (e.g. antibodies are proteins, CDR3 is a peptide, etc.). During patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See *In re Morris*, 127 F.3d 1048, 44 USPQ2d 1023 (Fed. Cir. 1997).

Regarding applicant's assertion that "antibodies are understood to bind a specific target and one skilled in the art would not expect one antibody to bind multiple proteins", it is respectfully noted that the same motif found in different proteins is what is being bound in the present invention. In addition, a monoclonal antibody (i.e. binds a single specific epitope/motif/antigen) may bind a single motif present in different proteins, polyclonal antibodies bind more than one motif/epitope/antigen, etc. In addition, it is respectfully noted that the presently claimed invention requires binding (i.e. encompassing nonspecific binding) and not specific binding, a specific Kd, etc.

Regarding applicants statement that there is "no substantiation of whether these hypothetical proteins are different proteins or whether they are merely variants of the same protein" (in Minden et al.), it is respectfully noted that present specification defines "different type" as including proteins and peptides differing in amino acid sequence, mass, posttranslation modifications and the like (i.e. encompassing variants, see page 5 lines 3-6 of the present specification).

"The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." See *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) and *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. See *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989), *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed.

Cir. 2005), and *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir.1998). Minden et al. teach methods comprising cleaving the protein with a proteolytic agent to produce peptide fragments, providing an array comprising a solution set of binding reagents, contacting the peptide fragments with the array to promote specific interactions, detecting the binding pattern, and comparison to a reference set wherein the "binding reagents" can be antibodies, Fv, scFv, Fab (i.e. array of antibodies; please refer to the entire specification particularly paragraphs 5, 29, 72). Minden et al. teach "a solution set of binding reagents may be designed to recognize a set of epitopes that are shared by many proteins in such a way that the set of epitopes covers and is capable of distinguishing proteins in the protein mixture" (see paragraph 40).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Kumar teaches antibody microarrays and interfacing the microarrays with MALDI-ToF (see paragraphs 27, 33, etc.). Barry et al. teach methods comprising protein fragmentation, contacting the peptide fragments with an antibody array/solid support, analysis of binding via mass spectrometry, and quantitation via MALDI-ToF (see abstract, pages 2, 3, 5, 6, 33-35, etc.).

New Rejections Necessitated by Amendment

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11, 13-14, 17, 21, 24, 26-27, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Minden et al. WO 02/086081 A2 (filing date April 22, 2002), Nelson et al. U.S. Patent 6,887,713 (effective filing date of March 11, 2000), Kumar U.S. Patent Application Publication 2002/0110835 published August 15, 2002, and Cardone et al. U.S. Patent Application Publication 2002/0076727 published June 20, 2002.

For present claim 1, Minden et al. teach methods of identifying a protein via assigning (i.e. separating) binding reagents to designated locations on an array, detecting the binding patterns, and comparing the binding pattern to a reference set (i.e. characterizing; please refer to the abstract, paragraphs [0005-0012], [0028-0032], [0035-0044], [0072-0074], [0077], [00117], Figures 1-11, and Table 1). In addition, Minden et al. teach that the molecular weight or mass of the binding reagents can be determined and that spectrometry can be utilized (please refer to paragraphs [0003-0004], [0030], [0036], [0048]; Figures 7-9). Furthermore, Minden et al. teach that more than one protein can have the same epitope thus the common epitopes (i.e. more than one) would bind to the same defined location (please refer to Figures 4A-4C and 5 and paragraphs 89-96). In addition, Minden et al. teach that the binding reagents can be antibodies (please refer to paragraphs [0029], [0056-0061], [0072]). Minden et al. discuss utilizing mass spectrometry in methods of identifying proteins (i.e. utilizing mass spectrometry in both homogenous and heterogeneous methods; paragraphs 3-4 and 136). Furthermore, Minden et al. teach heterogeneous protein mixtures including proteolytic cleavage of proteins (please refer to paragraphs 29-35). Moreover, Minden et al. teach that the protein mixture can be all of the

proteins in a given organism, proteome, organ, tissue, cell, organelle, or sub-cellular localization (see paragraph 35) and thus all of the proteins are not necessarily known. Minden et al. teach that the array can have 2-100 different proteins (please refer to paragraphs [0047], [0073-0074]).

For present claim 2, Minden et al. teach that the total protein content of a cell or tissue can be utilized as the protein mixture (please refer to paragraphs [0035], [0066]).

For present claims 3-6, Minden et al. teach that the protein mixture can be fragmented with various chemical or enzymatic methods including trypsin (please refer to paragraph [0037-0039], [0066], [00105], [00107], and Table 1).

For present claims 7-8 and 11, Minden et al. teach that trypsin cleavage forms a peptide or epitope (i.e. motif) with C-terminal lysine or arginine residues (please refer to Table 1 and paragraphs [0041-0045], [0049], [0054], [0063]).

For present claims 9-10, Minden et al. teach that the peptides or epitopes (i.e. motifs) can be at least three amino acids in length and can have at least two variable amino acids (please refer to paragraphs [0029], [0032], [0040-0046], [0054], [00113-00116]).

For present claim 13, Minden et al. teach that arrays can have different binding molecules at spatially addressable locations which bind to different binding reagents (please refer to paragraphs [0005], [0008], [0012], [0028], [0040]).

For present claim 14, Minden et al. teach that the protein mixture may comprise all (i.e. at least 10% of the peptides) of the proteins and that the epitopes cover the binding mixture (please refer to paragraph [0035], [0040]).

For present claim 21, Minden et al. teach that the proteins are compared to a reference set (i.e. characterizing; please refer to paragraphs [0005], [0028-0031], [0040]).

For present claim 27, Minden et al. teach that various binding reagents can be compared to a reference set or to other binding reagents (please refer to paragraphs [0005], [0030-0031, [0040], [0053]).

However, Minden et al. does not specifically teach determining the abundance of the proteins by the use of desorption mass spectrometry or collision induced dissociation mass spectrometry.

For present claims 1, 24, and 26, Nelson et al. teach analyzing complex biological mixtures utilizing "lab-on-a-chip" (i.e. chip-based microarrays) and MALDI-TOF (i.e. combination of both desorption mass spectrometry and collision induced dissociation mass spectrometry) wherein the proteins are quantified (i.e. abundance), internal reference standards are utilized, and determining the amount (i.e. abundance) of the proteins (please refer to the entire specification particularly the abstract; Figures 1, 4, 7, 8a-c, and 10a-c; column 1, lines 54-67; columns 2-3; column 4, lines 1-30; column 6, lines 52-67; column 8, lines 19-64; column 9, lines 13-35; columns 10-11 and 14-15; column 16, lines 1-10; column 17, lines 30-45). Nelson et al. discuss utilizing mass spectrometry in methods of identifying proteins (i.e. utilizing mass spectrometry in both homogenous and heterogeneous methods; columns 9-10). Nelson et al. teach utilizing MALDI-TOF for quantitative analysis including analysis of proteins from biofluids, heterogeneous analyte systems, sample comprising point mutations, etc. (i.e. heterogeneous sample; see column 2, lines 42-46; paragraph spanning columns 3-4; columns 5, 8-11, 15-16; Examples 3 and 6).

While Minden et al. discusses utilizing antibodies as binding reagents and immobilization of binding reagents onto arrays or substrates (see paragraphs 28 and 29), the specific examples provided by Minden et al. have the proteins, peptides, etc. immobilized on the array.

For present claims 1, 24, 26, and 27, Kumar teaches proteomic analysis comprising providing a substrate comprising distinct spots or deposits including an array of antibodies, exposing the antibody array to a sample containing proteins to allow capture of specific proteins, and subsequently interfacing the substrate (i.e. antibody array with bound proteins) with a MALDI-TOF instrument for identification of the proteins captured on the substrate/antibody array (please refer to the entire specification particularly abstract; paragraphs 27, 33, 37; Example 1).

However, Minden et al. does not specifically teach arrays comprising 150, 200, 250, 300 or more antibodies or fragments thereof.

For present claims 1, 17, and 50, Cardone et al. teach antibody microarryas comprising over 100, over 1000, over 2000 spots and analysis via mass spectrometry including MALDI (please refer to the entire specification particularly paragraphs 5-7, 18-26, 29, 30, 52-55, 66-71, 105, 107, 126, 130-132, 157, 158). In addition, mere scaling up of a prior art process capable of being scaled up, if such were the case, would not establish patentability in a claim to an old process so scaled (see *In re Rose* , 220 F.2d 459, 105 USPQ 237 (CCPA 1955), *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976), and *Gardner v. TEC Systems, Inc.*, 725 F.2d 1338, 220 USPQ 777 (Fed. Cir. 1984)).

The claims would have been obvious because the substitution of one known element (i.e. mass spectrometry providing mass information only as taught by Minden et al., smaller array

taught by Minden et al.) for another (i.e. mass spectrometry providing both mass and abundance information; MALDI-TOF as taught by Nelson et al. and Kumar, larger array taught by Cardone et al.) would have yielded predictable results (i.e. analysis of both mass and abundance at the same time, analysis of binding to more antibodies at one time) to one of ordinary skill in the art at the time of the invention and/or (b) the claim would have been obvious because a particular known technique (i.e. MALDI-TOF utilized to determine mass and abundance of proteins bound to antibody arrays) was recognized as part of the ordinary capabilities of one skilled in the art. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

Therefore, the teaching of Minden et al., Nelson et al., Kumar, and Cardone et al. render the presently claimed invention *prima facie* obvious.

Claims 1-11, 13-14, 17, 21, 24, 26-27, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Minden et al. WO 02/086081 A2 (filing date April 22, 2002), Barry et al. WO 0225287 (filed September 19, 2001), Kumar U.S. Patent Application Publication 2002/0110835 published August 15, 2002, and Mathew et al. U.S. Patent Application Publication 2003/0232396 filed February 21, 2003 (effective filing date of February 22, 2002).

For present claim 1, Minden et al. teach methods of identifying a protein via assigning (i.e. separating) binding reagents to designated locations on an array, detecting the binding patterns, and comparing the binding pattern to a reference set (i.e. characterizing; please refer to the abstract, paragraphs [0005-0012], [0028-0032], [0035-0044], [0072-0074], [0077], [00117], Figures 1-11, and Table 1). In addition, Minden et al. teach that the molecular weight or mass of the binding reagents can be determined and that spectrometry can be utilized (please refer to

paragraphs [0003-0004], [0030], [0036], [0048]; Figures 7-9). Furthermore, Minden et al. teach that more than one protein can have the same epitope thus the common epitopes (i.e. more than one) would bind to the same defined location (please refer to Figures 4A-4C and 5 and paragraphs 89-96). In addition, Minden et al. teach that the binding reagents can be antibodies (please refer to paragraphs [0029], [0056-0061], [0072]). Minden et al. discuss utilizing mass spectrometry in methods of identifying proteins (i.e. utilizing mass spectrometry in both homogenous and heterogeneous methods; paragraphs 3-4 and 136). Furthermore, Minden et al. teach heterogeneous protein mixtures including proteolytic cleavage of proteins (please refer to paragraphs 29-35). Moreover, Minden et al. teach that the protein mixture can be all of the proteins in a given organism, proteome, organ, tissue, cell, organelle, or sub-cellular localization (see paragraph 35) and thus all of the proteins are not necessarily known. Minden et al. teach that the array can have 2-100 different proteins (please refer to paragraphs [0047], [0073-0074]).

For present claim 2, Minden et al. teach that the total protein content of a cell or tissue can be utilized as the protein mixture (please refer to paragraphs [0035], [0066]).

For present claims 3-6, Minden et al. teach that the protein mixture can be fragmented with various chemical or enzymatic methods including trypsin (please refer to paragraph [0037-0039], [0066], [00105], [00107], and Table 1).

For present claims 7-8 and 11, Minden et al. teach that trypsin cleavage forms a peptide or epitope (i.e. motif) with C-terminal lysine or arginine residues (please refer to Table 1 and paragraphs [0041-0045], [0049], [0054], [0063]).

For present claims 9-10, Minden et al. teach that the peptides or epitopes (i.e. motifs) can be at least three amino acids in length and can have at least two variable amino acids (please refer to paragraphs [0029], [0032], [0040-0046], [0054], [00113-00116]).

For present claim 13, Minden et al. teach that arrays can have different binding molecules at spatially addressable locations which bind to different binding reagents (please refer to paragraphs [0005], [0008], [0012], [0028], [0040]).

For present claim 14, Minden et al. teach that the protein mixture may comprise all (i.e. at least 10% of the peptides) of the proteins and that the epitopes cover the binding mixture (please refer to paragraph [0035], [0040]).

For present claim 21, Minden et al. teach that the proteins are compared to a reference set (i.e. characterizing; please refer to paragraphs [0005], [0028-0031], [0040]).

For present claim 27, Minden et al. teach that various binding reagents can be compared to a reference set or to other binding reagents (please refer to paragraphs [0005], [0030-0031, [0040], [0053]).

However, Minden et al. does not specifically teach determining the abundance of the proteins by the use of desorption mass spectrometry or collision induced dissociation mass spectrometry.

Barry et al. teach methods of determining the binding and mass of trypsin digested proteins including antibodies from a cell including phage or tissue sample immobilized on an array (please refer to the abstract, pages 2-6, 21-30, Figures 3-6 and 8-10, Examples 2-3).

For present claim 1, Barry et al. teach determining the abundance of proteins via MALDI-TOF (i.e. mass; please refer to pages 5-6, page 32, lines 25-33, page 33, lines 21-37,

pages 34-35, Figures 3-6 and 8-10, Examples 2-3). Barry et al. discuss utilizing mass spectrometry in methods of identifying proteins (i.e. utilizing mass spectrometry in both homogenous and heterogeneous methods; pages 33-35). Barry et al. teach quantitative or semi-quantitative analysis via MALDI-TOF wherein the sample can include body fluid, tissue, or cell (i.e. heterogeneous; please refer to pages 3, 9, 21, 28, 32-34, 45-46).

For present claim 24, Barry et al. teach MALDI-TOF (i.e. matrix assisted laser desorption ionization-time of flight) mass spectrometry (i.e. combination of both desorption mass spectrometry and collision induced dissociation mass spectrometry or CID; page 35, line 7; please refer to pages 5-6, page 32, lines 25-33, page 33, lines 21-37, pages 34-35, Figures 3-6 and 8-10, Examples 2-3).

For present claim 26, Barry et al. teach determining the abundance of the protein via MALDI-TOF including proteins from any given starting material (i.e. unfragmented parent protein; please refer to page 3, lines 28-30; pages 5-6; page 32, lines 25-33; page 33, lines 21-37; pages 34-35; Figures 3-6 and 8-10, Examples 2-3).

While Minden et al. discusses utilizing antibodies as binding reagents and immobilization of binding reagents onto arrays or substrates (see paragraphs 28 and 29), the specific examples provided by Minden et al. have the proteins, peptides, etc. immobilized on the array.

For present claims 1, 24, 26, and 27, Kumar teaches proteomic analysis comprising providing a substrate comprising distinct spots or deposits including an array of antibodies, exposing the antibody array to a sample containing proteins to allow capture of specific proteins, and subsequently interfacing the substrate (i.e. antibody array with bound proteins) with a MALDI-TOF instrument for identification of the proteins captured on the substrate/antibody

array (please refer to the entire specification particularly abstract; paragraphs 27, 33, 37; Example 1).

However, Minden et al. does not specifically teach arrays comprising 150, 200, 250, 300 or more antibodies or fragments thereof.

For present claims 1, 17, and 50, Mathew et al. teach antibody microarryas comprising 5, 10, 20, 50, 100, 250, 500 or more spots and analysis via SELDI-ToF (please refer to the entire specification particularly the abstract; Figure 1, paragraphs 11, 12, 15, 27, 28, 45, 46, 82, 83, 89, 97, 98, 101-107, 111, 112, 115). In addition, mere scaling up of a prior art process capable of being scaled up, if such were the case, would not establish patentability in a claim to an old process so scaled (see *In re Rose* , 220 F.2d 459, 105 USPQ 237 (CCPA 1955), *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976), and *Gardner v. TEC Systems, Inc.*, 725 F.2d 1338, 220 USPQ 777 (Fed. Cir. 1984)).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of identifying proteins taught by Minden et al. with the MALDI-TOF analysis taught by Barry et al.

One having ordinary skill in the art would have been motivated to do this because Barry et al. teach that the use of mass spectrometry and MALDI-TOF provide semi-quantitative and quantitative results for protein microarrays (please refer to page 1, lines 20-26 and 34-37; page 2, lines 1-24; page 3, lines 5-30; Examples 2-3).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the method of identifying proteins taught by Minden et al. with the MALDI-TOF

analysis taught by Barry et al. because of the examples provided by Barry et al. show that trypsin digested antibody arrays can be quantitated via MALDI-TOF (please refer to Examples 2-3).

The claims would have been obvious because the substitution of one known element (i.e. mass spectrometry providing mass information only as taught by Minden et al., small array taught by Minden et al.) for another (i.e. mass spectrometry providing both mass and abundance information; MALDI-TOF as taught by Barry et al. and Kumar, large array taught by Mathew et al.) would have yielded predictable results (i.e. analysis of both mass and abundance at the same time, analysis of more antibody binders) to one of ordinary skill in the art at the time of the invention and/or (b) the claim would have been obvious because a particular known technique (i.e. MALDI-TOF utilized to determine mass and abundance of proteins bound to antibody arrays) was recognized as part of the ordinary capabilities of one skilled in the art. See KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007).

Therefore, the modification of the method of identifying proteins taught by Minden et al. with the MALDI-TOF analysis taught by Barry et al. and Kumar and the larger antibody array taught by Mathew et al. render the instant claims *prima facie* obvious.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is (571)272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amber D. Steele/
Primary Examiner, Art Unit 1654